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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,100	01/31/2005	John W. Adams	27.US2.PCT	4553

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ARENA PHARMACEUTICALS, INC.
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EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,100	ADAMS ET AL.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-131* is/are pending in the application.

4a) Of the above claim(s) *97-121* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-96 and 122-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 January 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/25/2006, 07/14/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignment*.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, directed to an isolated polypeptide set forth in SEQ ID NO: 3 and congestive heart failure (as disease species) in the reply filed on 09/26/2006 is acknowledged. The traversal is on the ground(s) that the restriction requirement is based on an erroneously drawn special technical feature. This is not found to be persuasive for the reasons set forth in the previous office action (mailed on 03/27/2006).

Applicants argue that the amino acid sequences recited in the claims share a significant structural element and thus do not form a proper basis for restriction. Applicants' argument is partially persuasive. In view of the fact that the amino acid sequence of SEQ ID NO: 2 differs from the amino acid sequence of SEQ ID NO: 3 by a single amino acid at residue 425, the two amino acid sequences will be examined together. However, SEQ ID NO: 5 does not share a significant common structure with SEQ ID NO: 2 and 3, and it will not be considered.

Applicants argue that the election of species relating to diseases recited in the claims is improper as these share the special technical feature of RUP41 GPCR's association with cardioprotection. This has been fully considered, but is not deemed to be persuasive because these species do not share a common pathological

feature. In addition, there is sufficient evidence showing that RUP41 GPCR is associated with cardioprotection.

Applicants request for rejoinder of Groups I-VI and XI; Groups VII and VIII; and Groups XIII and XI. This is not found persuasive because the invention groups are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept. Thus, unity of invention is lacking and restriction is appropriate.

Applicants argue that if the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions. The Examiner agrees. However, search and examination more than one invention group places an undue burden on the office.

The requirement is still deemed proper and is therefore made FINAL.

2. Applicants amendment filed on 09/26/2006 has been entered. Claims 85-131 are pending. Claims 85-96 and 122-131 are currently under consideration. All other claims are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made wit traverse in the reply filed on 09/26/2006.

Information Disclosure Statement

3. The information disclosure statements filed on 04/25/2006 and 07/14/2005 have been considered by the examiner.

Drawings

4. The drawings filed on 01/31/2005 are objected to because the drawings are not clear enough for the examiner to evaluate the data. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Rejections—35 USC § 101

5. 35 U.S.C. §101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 85-96 and 122-131 are rejected under 35 U.S.C. §101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 85-96 and 122-131 are drawn to a method of identifying a candidate compound as a modulator of cardioprotection, comprising contacting a candidate compound with a GPCR comprising SEQ ID NO: 2, SEQ ID NO: 3, or a fragment or variant thereof. The claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention which does not require further research.

The specification discloses the RUP41 GPCR polypeptides set forth in SEQ ID NO: 2 and 3, and a reduced level of RUP41 transcripts in congestive heart failure (Example 14). The specification also asserts that over-expression of RUP41 promotes survival of neonatal rat ventricular myocytes (NRVMs; Example 16) and rescues NRVMs from hypoxia/reoxygenation (Example 17). However, since the in vitro assays described in Examples 16 and 17 were performed in serum free conditions, these effects do not appear to be resulted from the activation of the receptor by a natural ligand. There is no evidence disclosed in the specification or on record showing that there is a causative link between the RUP41 GPCR polypeptide set forth in SEQ ID NO: 2 (or SEQ ID NO: 3) and congestive heart failure; there is no evidence showing whether an agonist or antagonist can be used in treating congestive heart failure; there is no disclosure of examples of the candidate

compounds which can be used for treating the disease or the identifying characteristics for recognizing that a candidate compound is useful for treating the disease.

While the prior art (U.S. 6,555,339 B1) teaches a GPR22 polypeptide, which is 100% identical to SEQ ID NO: 2 (see sequence alignment attached in the previous office action) and 99.5% identical to the amino acid sequence of SEQ ID NO: 3 (see sequence alignment), and the preparation of a non-endogenous and constitutively activated form of the GPR22 (F312K), the prior art is silent regarding the role of the RUP41 polypeptides set forth in SEQ ID NOS: 2 and 3 in congestive heart failure. The prior art does not teach the ligand of the GPR22 and the physiological role of the GPR22.

Clearly, it will require further research for an artisan to confirm a "real world" context of use, that is, to determine the biological functions of the RUP41 polypeptides and to determine the causative link between the RUP41 polypeptides and congestive heart failure before an artisan is able to practice the method of screening for a compound that is useful for treating congestive heart failure. However, such further research is not permitted under 35 U.S.C. §101. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the claimed invention is not supported by a specific, substantial, and credible asserted utility.

7. Claims 85-96 and 122-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Furthermore, even if the claimed method were to have a patentable utility, the instant disclosure would not be found to be enabling for the full scope of the claimed invention.

Claims 85-96 and 122-131 are drawn to a method of identifying a candidate compound as a modulator of cardioprotection, comprising contacting a candidate compound with a GPCR comprising SEQ ID NO: 2, SEQ ID NO: 3, an amino acid sequence with at least 90% identity to SEQ ID NO: 2 or SEQ ID NO: 3, or a fragment or variant thereof. Thus, the claims are drawn to a method of using a genus of GPCR polypeptides. The claims do not recite any structural limitation for the variants, homologues, or fragments. The instant disclosure fails to provide sufficient guidance and/or working examples to make and use the genus of polypeptides recited in the claims and thus fails to practice the instantly claimed methods.

Moreover, the claims recite a method of identifying a candidate compound as a modulator of cardioprotection. A modulator can be either an agonist or an antagonist. If an agonist is capable of treating congestive heart failure, an antagonist will not be capable of treating the same disorder. Only a compound that reduces symptoms of congestive heart failure is capable of treating congestive heart failure.

Furthermore, the specification fails to disclose the ligand that binds and

activates the RUP41 polypeptides set forth in SEQ ID NOS: 2 and 3. Without a known ligand, one skilled in the art would not be able to practice the instantly claimed method using a polypeptide that is not constitutively active.

Finally, claims 87 and 88 recite "prevention of a cardiovascular disorder" or "prevention of an ischemic heart disease". It is known in the art that while a cardiovascular disorder or an ischemic heart disease may be treated; it cannot be prevented.

Claim Rejections—35 USC § 112, 1st paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 85-96 and 122-131 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

Claims 85-96 and 122-131 are drawn to a method of identifying a candidate compound as a modulator of cardioprotection, comprising contacting a candidate compound with a GPCR comprising SEQ ID NO: 2, SEQ ID NO: 3, an amino acid sequence with at least 90% identity to SEQ ID NO: 2 or SEQ ID NO: 3, or a fragment or variant thereof. Thus, the claims are drawn to a method of using a genus of GPCR polypeptides. The claims do not require that the amino acid sequences possess any particular biological activity, nor any particular conserved structure, nor other disclosed distinguishing feature.

The instant disclosure of two human RUP41 GPCR polypeptides set forth in SEQ ID NO: 2 and 3 and a mouse RUP41 GPCR polypeptide set forth in SEQ ID NO: 5 do not adequately support the scope of the recited genus, which encompasses a substantial variety of homologues or variants of the polypeptides of SEQ ID NOS: 2 and 3. A description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). While disclosing the amino acid sequences of SEQ ID NOS: 2 and 3, the instant disclosure fails to provide sufficient description information, such as definitive structural or functional features of the recited genus of polypeptides. There is no description of the conserved regions that are critical to the structure and function of the genus recited. There is no description of the sites at which variability may be

tolerated and there is no information regarding the relation of structure to function.

The prior art (U.S. 6,555,339 B1) teaches a GPR22, which is 100% identical to SEQ ID NO: 2 (see sequence alignment attached in the previous office action) and 99.5% identical to the amino acid sequence of SEQ ID NO: 3 (see sequence alignment). The prior art (U.S. 6,555,339 B1) also teaches preparation of a non-endogenous and constitutively activated form of the GPR22 by site-directed mutagenesis (F312K). However, the prior art does not teach the ligand of the GPR22 and the physiological role of the GPR22 and does not provide compensatory structural or correlative teachings to enable one skilled in the art to identify the encompassed polypeptides as being identical to those instantly claimed.

Moreover, the specification discloses the amino acid sequence of a first allele of human GPR22, SEQ ID NO: 2, and a second allele of human GPR22, SEQ ID NO: 3. However, there is no description of other mutational sites that exist in nature, and there is no description of how the structure of the polypeptides of SEQ ID NOS: 2 and 3 relates to the structure of different variants. The general knowledge in the art concerning variants does not provide any indication of how the structure of one variant is representative of other unknown variants having concordant or discordant functions. The nature of variants is such that they are variant structures where the structure and function of one does not provide guidance to the structure and function of others.

Due to the breadth of the genus of the polypeptides recited in the claims and lack of the definitive structural or functional features of the recited genus, one skilled

in the art would not recognize from the disclosure that the applicant was in possession of the genus of the polypeptides, and thus the instantly claimed methods.

Claim Rejections—35 USC§ 112, 2nd paragraph

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 85-96 and 122-131 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 85 and 88 recite "...hybridizes under stringent conditions...". However, neither the specification nor the art provides an unambiguous definition for the term, the claims are indefinite.

Claims 85 and 88 recite "wherein inhibition or stimulation of said receptor functionality is indicative...". It is unclear what functionality is referred.

Claim 85-96 and 122-131 are indefinite because the steps of the method do not necessarily achieve the goal set forth in the claim preamble. The claimed methods would not be able to identify a modulator of cardioprotection. A modulator of the invention can be shown to be cardioprotective using the in vivo rat model (see Example 18).

Claim Rejections—35 U.S.C. §102 (b)

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 85-93, 95, 96, 122-129, and 131 are rejected under 35 U.S.C. 102(e) as being unpatentable over Liaw et al. (U. S. Patent No. 6,555,339 B1, 102(e) date: October 13, 1998).

Liaw et al. teach a GPR22 polypeptide that is 100% identical to SEQ ID NO: 2 (see sequence alignment attached in the previous office action mailed on 03/27/2006) and 99.5% identical to the amino acid sequence of SEQ ID NO: 3 (see sequence alignment). Liaw et al. also teach preparation of a constitutively activated form of the GPR22 by site-directed mutagenesis (F312K; Table B).

Liaw et al. teach GPCR screening assays for direct identification of candidate compounds as inverse agonists, agonists or partial agonists using a constitutively active form of human GPCRs (columns 13 and 14). These agonists would have the properties of the modulators recited in the claims since they are identified in the identical methods using the same GPCR polypeptides. Liaw et al. further teach that candidate compounds can be formulated into pharmaceutical composition using pharmaceutically acceptable carriers (column 14, lines 50-57).

Liaw et al. teach measurement of GTPγS binding to a membrane (line29 of column 13; see also GTPγS assay of Example 4), measurement of the level of a second messenger, such as cAMP (column 13 and 14; see also Adenylyl Cyclase of

Example 4). Liaw et al. further teach expression of endogenous and mutated receptor in mammalian host cells and yeast host cells (Example 3).

Accordingly, the teachings of Liaw et al. meet the limitations of claims 85-93, 95, 96, 122-129, and 131.

Claim Objections—Minor Informalities

14. Claims 85-96 and 122-131 are objected to because they recite non-elected subject matter. Claims 85 and 88 are objected to because each claim recites "or a fragment or variant hereof". It is not clear how such a recitation is related to the Markush group. Appropriate correction is required.

Conclusion

15. No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

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PRIMARY EXAMINER

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December 10, 2006